# RESEARCH AND LICENSE AGREEMENT

This Agreement is made and entered into as of the 11th day of June, 1993 (the "Effective Date") between SHEARWATER POLYMERS, INC., a corporation having a principal place of business at 2130 Memorial Pkwy S.W., Huntsville, Alabama ("Shearwater") and SYNERGEN, INC., a Delaware corporation ("Synergen").

WHEREAS, the parties intend, so far as is commercially practicable, that Shearwater develop the capacity to supply Synergen's requirements for polyethylene glycol derivatives for the manufacture of soluble, pegylated proteins for pharmaceutical applications, first in experimental and then in commercial quantities. The parties have previously entered into an interim supply agreement for two kilograms of peg-20K-*bis*-vinylsulfone. Synergen now desires to obtain additional supplies of peg-20K-*bis*-vinylsulfone and to sponsor research for the development of additional polyethylene glycol derivatives to develop soluble, pegylated proteins for pharmaceutical applications. Shearwater is willing to perform such research and to develop the capacity to supply Synergen's requirements for polyethylene glycol derivatives.

NOW, THEREFORE, in consideration of the foregoing and the covenants and promises contained in this Agreement, the parties agree as follows:

## 1.0 DEFINITIONS

1.1 "Affiliate" shall mean a corporation or other business entity that directly or indirectly controls, is controlled by, or that controls or is under the common control with a party to this Agreement. For this purpose, the meaning of the term "control" shall include without limitation ownership of more than fifty percent (50%) of the voting shares or interest of such entity.

1.2 "Confidential Information" or "Confidential Material" shall include biological and biochemical materials, including but not limited to natural and recombinant proteins and polypeptides, clones, progeny, derivatives and genetic materials or information taken or derived from any of the foregoing; studies, test results and other information regarding human and animal trials, formulations, toxicology studies, stability data, manufacturing processes, product quality controls and marketing; applications to governmental agencies and related information in connection with drug approval or patent process until published; engineering data, designs, specifications or other information relating to the manufacture of pharmaceuticals; methods for making preparing and analyzing PEG Derivatives, methods for attachment of PEG derivatives to polypeptides; and commercial, financial and scientific information, whether written or oral, including but not limited to trade secrets, know-how and technical and non-technical data. Confidential Information shall not include information that the receiving party can established by competent proof: (a) was already known to the receiving party, other than under an obligation of confidentiality, at the time of its disclosure to the receiving party; (b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the receiving party; (c) became generally available to the public

or otherwise part of the public domain after its disclosure to the receiving party and other than through any act or omission of the receiving party in breach of this Agreement; or (d) was subsequently lawfully disclosed to the receiving party by a third party who had not violated an obligation not to disclose such information to others.

1.3 "Field" shall mean all applications for soluble proteins for pharmaceutical purposes.

1.4 "Inventions" shall include discoveries, concepts, ideas, whether patentable or not, arising out of Sponsored Research, including but not limited to compounds, processes, methods, formulas, techniques, microorganisms, strains, and cultures as well as improvements thereof or know-how related thereto.

1.5 "Know-how" shall mean all technologies and information arising out of Sponsored Research in the possession of and proprietary to a party, except technologies and information within the scope of the party's Patent Rights. Know-how shall mean trade secrets and technical and non-technical data relating but not limited to methods, prototypes, techniques, compounds, materials, commercial, scientific, financial and marketing information and data, and engineering data, designs and specifications.

1.6 "Patent Rights" shall mean all patents and applications therefor, throughout the world, as well as invention certificates, substitutions, extensions, reissues, renewals, divisions, continuations, or continuations-in-part thereof or therefor arising out of Sponsored Research.

1.7 "PEG Derivative" shall mean any derivative of polyethylene glycol or related polyethers which are either homobifunctional, heterobifunctional or multifunctional in nature and which can be derivatized to a soluble polypeptide and which are proprietary to Shearwater, including peg-20K-*bis*-vinylsulfone, or arising out of Sponsored Research, including, but not limited, to peg-20K-*bis*-amine and peg-20K-*bis*-maleimide.

1.8 "Sponsored Research" shall mean all research funded by Synergen and conducted by Shearwater pursuant to Section 3.0 below and as outlined in Exhibit A, as well as the joint research relating to PEG Derivatives pursuant to the letter agreement dated August 12, 1992, between the parties hereto.

1.9 "Total Net Price" shall mean gross invoiced price less all applicable discounts, taxes, and freight, handling and insurance charges.

1.10 "Valid Claim" shall mean patents or patent applications relating to PEG Derivatives in which Shearwater has an ownership interest and which have not been disclaimed without possibility of reinstatement or held unenforceable by a decision of the relevant government authority beyond right of review.

## 3.0 SPONSORED RESEARCH

3.1 Scope of Research. Shearwater shall conduct research on PEG Derivatives as contemplated in the Research Plan contained in Exhibit A or as it may be amended by mutual, written agreement of the parties. The research shall be sponsored by Synergen for a term of one year commencing on the Effective Date and shall be extendable for additional one year terms upon mutual, written agreement of the parties.

3.3 Reporting. During the term of Sponsored Research or any extensions thereof, Shearwater shall deliver to Synergen monthly progress reports and quarterly reviews containing a detailed summary of its research efforts and data generated during the quarter. Synergen shall have the right to review and copy original laboratory notebooks and data or copies thereof coming within the scope of Sponsored Research.

[redacted]

3.5 Exclusivity. During the pendency of Sponsored Research and for six months after the expiration or termination thereof, Shearwater shall not work in collaboration with a third party on the development of sulfhydryl-specific PEG derivatives for protein modification for applications in the Field.

3.6 Synergen Independent Research. Shearwater acknowledges that Synergen is engaged in independent research activities relating to the pegylation of polypeptides for applications in the Field. Nothing in this Agreement shall be interpreted to limit or otherwise affect Synergen's ability to engage in such independent research activities for the development of commercial products.

## 4.0 INVENTIONS AND PATENTS

4.1 Ownership. Each party shall retain title to Inventions, Patents Rights, Confidential Information and Know-how owned by it as of the Effective Date, or made or developed solely by it during the course of Sponsored Research. Inventions and Know-how made or developed by at least one employee or agent of each party within the scope of Sponsored Research will be jointly owned by Synergen and Shearwater. Ownership shall be governed by the United States laws of inventorship. Disputes regarding inventorship shall be resolved by mutual agreement of the parties' patent counsels. Disputes as to inventorship not resolvable by the parties' patent counsels shall be submitted for decision by a qualified patent counsel mutually acceptable to the parties. Each party will undertake to ensure its employees or contractors assign ownership in any such invention or know-how to it.

4.2 Filing, Prosecution and Maintenance

(a) Synergen, at its sole option, may assume full cost and responsibility for preparing, prosecuting, and maintaining Patent Rights in the Field regardless of ownership. Shearwater shall disclose to Synergen in writing any invention promptly after conception of such Invention and shall promptly provide a copy of any such disclosure to Synergen. Shearwater will assist in securing Patent Rights for Inventions as reasonably requested by Synergen. All costs incurred by Shearwater in assisting

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Synergen, except costs associated with legal advice sought by Shearwater in connection with such assistance, shall be borne by Synergen. Synergen shall promptly provide a copy of any jointly owned or Shearwater-owned patent application to Shearwater. Shearwater shall have the right to monitor the preparation, prosecution and maintenance of any such application.

(b) Synergen reserves the right not to file, prosecute or maintain any or all Patent Rights in which event it shall notify Shearwater within sixty (60) days of the time the invention is completed and sufficiently disclosed to Synergen [redacted] application can be filed and in sufficient time prior to the abandonment [redacted] or lapse of an issued patent to enable Shearwater, at its sole option, to file [redacted] or maintain such Patent Rights at its own expense and Synergen agrees to [redacted] for such preparation, prosecution and maintenance of any such patent or application. Synergen continue to owe royalties thereunder in connection with paragraph 4.2 above.

4.3 Enforcement of Patent Rights. Synergen shall have the right, but not the obligation, to be responsible for all infringement actions relating to Patent Rights in the Field. If Synergen elects not to pursue an infringement action, it shall so notify Shearwater and Shearwater may do so at its own expense. In any event, the party not initiating the infringement action shall upon request assist the initiating party to the extent reasonably necessary, and at the expense of the initiating party; provided, however, such assistance shall not include payment of fees or charges incurred in pursuing an infringement action. Any recoveries made shall first be allocated to the initiating party to cover its costs directly attributable to bringing the action, second, to pay any and all royalties owed under this agreement, and third, to the initiating party.

IN WITNESS WHEREOF, the parties hereto have as of the Effective Date duly executed this Agreement, including the attached Exhibit which is incorporated herein and made a part of this Agreement.

SYNERGEN, INC.

By: Gregory B. Abbott

Name: Gregory B. Abbott

Title: Executive Vice President

SHEARWATER POLYMERS, INC.

By: J. Milton Harris

Name: J. Milton Harris, Ph.D.

Title: President

SYNERGEN

1885 33rd Street
Boulder, Colorado 80301-2546
303-938-6200
303-441-5535 FAX

12/3/92

**Synergen-Shearwater Polymers Joint Research: Privileged and confidential material.**

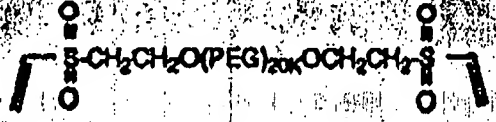
**Exhibit A**

Synergen and Shearwater Polymers shall enter into a joint collaboration for the study and development of novel sulfhydryl-specific PEG-protein linking agents. The goal of this work is to develop derivatives that provide high reactivity and selectivity for modification of the sulfhydryl side chain of cysteine residues in proteins. Ideally such derivatives should provide stable linkages upon reaction, be easily and inexpensively synthesized, and the processes for their preparation be amenable to scale up.

*Research priorities to achieve the goal of this work:*

1. First, we will incorporate the vinylsulfone group in the preparation of heterobifunctional PEG reagents. The purpose of this is to define suitable chemistry which will allow the sequential and controlled addition of pharmacophors to each end of the linear PEG chain. An entire new family of pharmaceuticals (heterodumbbells) can emerge from this work (re: B. Thompson 8/21/93, new project proposal on cell anchored pharmaceuticals.). Please refer to the scheme of "Membrane anchored probes" and "Heterobifunctional PEG's" for a generic discription of structure. The synthesis of these heterobifunctional PEG linkers is unknown in the literature. We only need to prepare small specimens (ca. 1 g) to enable the preparation of some prototypical pharmaceuticals. This work will also give us the opportunity to exploit our findings of the vinylsulfone functionality. Various combinations can be envisioned: vinylsulfone—β-chlorosulfone; NHS-ester—vinylsulfone; isothiocyanate—vinylsulfone; homo-pairs; etc. From these, numerous pharmaceuticals candidates: Protein—Protein; Protein—Drug; Protein—Cell; Drug—Drug; etc.

2. Second, we will examine a series of PEG's containing carbon-carbon double bonds designed to react by Michael addition. Examples of such compounds include PEG-maleimide and PEG-vinylsulfone, which provide selective reaction toward sulfhydryl groups by functioning as Michael electrophiles. Hence, as a first step in protecting the research findings of the PEG-*bis*-vinylsulfone (structure below) we would like to investigate the structural variants and derivatives that may exist for this group.



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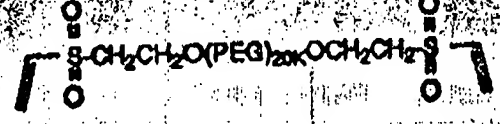
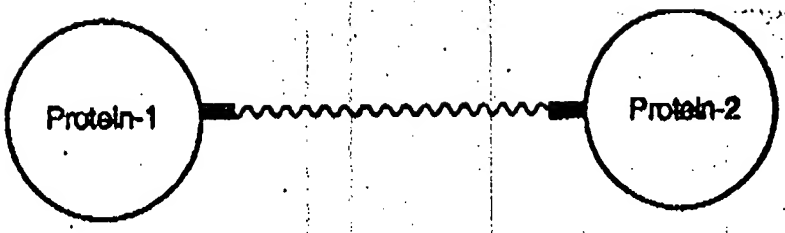


4. Fourth, we will examine a few electrophilic PEG's that are susceptible to displacement reactions by sulfhydryls and others nucleophiles. Examples of such compounds include N-hydroxysuccinimides, cyanuric chloride, triflates, tresylates, etc. While such compounds are not noted for selectivity toward sulfhydryls, detailed investigations have not been conducted and some study is warranted. Hence we will give this area a low priority.

This research will first address and exploit the preparation and reactivities of heterobifunctional PEG reagents. For novel linking groups, monofunctional reagents based on low molecular weight PEG's will be prepared for the initial assessment of the chemical synthesis, and for evaluation of the coupling reaction. This will offer some advantage over large molecular weight materials. As a measurement of specificity for the new heterobifunctional and monofunctional linkers, the compounds will be characterized in terms of their reactivity and selectivity toward model small molecules (such as β-mercaptoethanol and β-aminoethanol), in small molecule competition studies, and then with proteins. TNBS and Ellman's assays will be used for this and are already in place at Synergen and Shearwater. We will design assays for the analysis of groups labeling residues other than amine or mercaptan as appropriate. Linkage stability will also be examined. Representative prototypes of α,ω-*bis*-derivatives will then be prepared and forwarded to Synergen when the new monofunctional derivatives first show promise as protein modifiers.




***Examples:***

1. IL-2 synthetic receptor. (Heterodumbbell)
2. TNFbp——IL-1ra. (Heterodumbbell)

***Possibilities:***

1. NHS-esters-vinylsulfone
2. Maleimide-vinylsulfone

4. Homo-pairs.